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WOOD, PHILLIPS, KATZ, CLARK & MORTIMER
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EXAMINER	
SAKELARIS, SALLY A	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,926	SCHATZ, OCTAVIAN	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-36* is/are pending in the application.

4a) Of the above claim(s) *35-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 21-34, drawn to a method for the production of a nucleic acid molecule is acknowledged. Claims 35 and 36 are withdrawn as non-elected subject matter. Claims 21-34 are examined herein.

Priority

Acknowledgement of claim to foreign priority of German Application, 19925862.7 filed 6/07/1999 under 35 U.S.C. 119(a)-(d) has been made and applicant should note that the certified copy and translation of this foreign priority document has been received and as a result the claim to foreign priority under the same has been granted.

Claim Objections

Claims 25-34 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, claims 25-34, in the interest of furthering prosecution will be examined such that they are read to depend solely from independent claim 21. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 21-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 21-34 are rejected over the recitation of "adding an additional oligonucleotide" in step ab) and bb) of claim 21. It is not clear to what the additional oligonucleotide is being added. It is suggested that this step be amended in order to clarify to what solution, reaction, composition, is being added to.

B. Claims 21-34 are rejected over the recitation of "cannot bind the matrix" in steps ab) and bb) of claim 21. It is not clear what, if any, structural limitations are being imposed on the oligonucleotide that cause its inability to bind the matrix. Appropriate clarification is suggested.

C. Claims 21-34 recites the limitation "the orientation determined" in steps ac), bc), and c) of claim 21. There is insufficient antecedent basis for this limitation in the claim. It is not clear to what orientation the claim refers. Appropriate correction is suggested.

D. Claims 21-34 recite the limitation "the blockage" in steps ac), bc), and c) of claim 21. There is insufficient antecedent basis for this limitation in the claim. It is not clear to what blockage the claim refers. Appropriate correction is suggested.

E. Claims 21-34 recite the limitation "the ends" in steps ac), bc), and c) of claim 21 and claim 31's "ends". There is insufficient antecedent basis for this limitation in the claim. It is not clear to what ends the claim refers. Furthermore, it is not clear if the claim is referring to each and every end of both oligonucleotides, or only one end of each oligonucleotide(the end without the recognition sequence). Appropriate correction is suggested.

F. Claims 21-34 are rejected over the recitation of "removing non-consumed reactants and enzymes" in steps ad), bd), and d) of claim 21. First, there is insufficient antecedent basis for this limitation in the claim because the preceding steps do not recite "reactants". Second, it is not clear when the reactants and enzymes were added to allow them to now be removed. Third, it is not clear which reactants and enzymes will be considered as "non-consumed". Appropriate clarification is suggested.

G. Claims 21-34 are rejected over the recitation of "the reaction mixture" in steps af), bf), and f) of claim 21 and claim 24. There is insufficient antecedent basis for this limitation in the claim because preceding steps do not recite or describe a "reaction mixture". It is not clear to what reaction mixture the claim refers as the only reactant that has been added are oligonucleotides but just two have been added and were not in a mixture of any sort upon their addition. Appropriate clarification is suggested.

H. Claims 21-34 are rejected over the recitation of "the elongated oligonucleotide from step aa) obtained in step ae)" in steps af), bf), and f) of claim 21. First, there is insufficient antecedent basis for this limitation in the claim. Second, it is not clear to what elongated oligonucleotide the claim refers, i.e. how could the oligonucleotide be from step aa) and obtained in step ae)? Finally, it is not clear if the claim refers to the oligonucleotide that is coupled to the solid matrix(step ab)) or to ligation product from step ae) that originates in step ac)? Appropriate clarification is suggested.

I. Claims 22-34 are rejected over the recitation "wherein the oligonucleotide used in step ab) or bb) is a nucleic acid molecule produced by the method as claimed in claim 21". It is not clear how a product of claim 21 could also be a required reagent in the preliminary steps of the

same claim. It is therefore not clear how the claim could be initially practiced, without the product("nucleic acid molecule produced") to be used in steps ab) and bb). Appropriate clarification is suggested.

J. Claims 33-34 are rejected over the recitation of "wherein the various type IIS restriction endonucleases are replaced by ribozymes" since claim 21 requires type IIS enzymes, and claims depending therefrom also require type II enzyme. Claim 33 improperly depends from claim 21 as it is not clear how this claim could be dependent of claims 21-32 and still include a replacement by ribozymes in the previous method steps. Applicant should note that such a limitation must be made in the alternative in the independent claim, its present placement creates an indefinite claim. Appropriate clarification is suggested.

K. Claims 29-34 are rejected over claim 29's recitation of a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance,

claim 29 recites the broad recitation of bead, and the claim also recites preferably made of glass or polystyrene which are the narrower statements of the limitation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

It should be noted that the art has been applied in view of the indefiniteness rejections made above and as best as the examiner can understand the invention being claimed.

2. Claims 21-27, 29-32, and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over DuBridge et al.(US Patent 5,888,737) in view of Church et al.(US Patent 6,485,944).

With regard to claim 1 DuBridge et al. teach a method for the production of a nucleic acid molecule comprising the steps

a) providing an oligonucleotide which is prepared by the following steps:

aa) coupling one end of an oligonucleotide to a solid matrix(Col.19 lines 1-60) wherein the coupling is effected by means of a modification such as highly crosslinked polystyrene beads providing bead-polynucleotide conjugates(Col. 19 lines 65-67 and Col. 20 line 3), and the polynucleotide contains a recognition sequence for a type IIS restriction enzyme(Col. 11 lines 28-37 for example) which cleaves outside its recognition sequence. The reference teaches that "prior to ligation, ends of polynucleotides to be analyzed are prepared by digesting them with

one or more restriction endonucleases that produce predetermined cleavages, usually having 3' or 5' protruding strands"(Col. 6 lines 21-25).

ab) adding an additional oligonucleotide(Col. 13 and 14 any one of A1, A2, A3 or the "stepping adaptor" references) which is at least partially double stranded(col. 3 line 26 for example) and contains a different recognition sequence than in step aa) for a type IIS restriction enzyme which cleaves outside its recognition sequence, whereby this oligonucleotide cannot bind the matrix, in their teaching of "many target polynucleotides in parallel" and "attaching a first oligonucleotide tag from a repertoire of tags to each polynucleotide in a population of polynucleotides" and "further sampling the population of polynucleotides such that substantially all different polynucleotides in the population have different first oligonucleotide tags attached"(See Col. 11-12, and figures 2A-3E)

ac) ligating the oligonucleotide from steps aa) and ab) in the orientation determined by the blockage of the end that are not to be ligated(See Fig. 2A-3E for example and Col. 6 lines 35-55).

ad) removing non-consumed reactants and enzymes(Col. 20 lines 51-57) in a wash with TE(pH 8.0).

ae) cleaving the ligation product from step ac) with a type IIS restriction enzyme which cleaves outside its recognition sequence whereby the cleavage occurs in the nucleic acid sequence of the oligonucleotide from step ab)(Col. 13 and 14) in the reference's teaching of the "target polynucleotides cleaved with the nuclease of the stepping adaptor may be ligated to a further set of cleavage adaptors A4, A5, and A6 which may contain nuclease recognition sites

that are same or different than those contained in cleavage adaptors A1, A2, and A3"(Col. 14 lines40-45).

af) separating the reaction mixture from the elongated oligonucleotide from step aa) obtained in step ae) in their teaching in Col. 22 lines 20-21 that following cleave the beads are washed 3 times in TE (ph 8.0).

ag) repeating steps ab) to af) at least once is taught throughout the reference and specifically in DuBridge's claim 4 teaching that the process be "repeated one or more times"(Col. 25 and claim 4).

b) providing an oligonucleotide which is prepared by the following steps:

ba) coupling one end of an oligonucleotide to a solid matrix(Col.19 lines 1-60) wherein the coupling is effected by means of a modification such as highly crosslinked polystyrene beads providing bead-polynucleotide conjugates(Col. 19 lines 65-67 and Col. 20 line 3) and the polynucleotide contains a recognition sequence for a type IIS restriction enzyme(Col. 11 lines 28-37 for example) which cleaves outside its recognition sequence. The reference teaches that "prior to ligation, ends of polynucleotides to be analyzed are prepared by digesting them with one or more restriction endonucleases that produce predetermined cleavages, usually having 3' or 5' protruding strands"(Col. 6 lines 21-25).

bb) adding an additional oligonucleotide(Col. 13 and 14 any one of A1, A2, A3 or the "stepping adaptor" references) which is at least partially double stranded(col. 3 line 26 for example) and contains a different recognition sequence than in step ba) for a type IIS restriction enzyme which cleaves outside its recognition sequence, whereby this oligonucleotide cannot bind the matrix, in their teaching of "many target polynucleotides in parallel" and "attaching a

first oligonucleotide tag from a repertoire of tags to each polynucleotide in a population of polynucleotides" and "further sampling the population of polynucleotides such that substantially all different polynucleotides in the population have different first oligonucleotide tags attached"(See Col. 11-12, and figures 2A-3E)

bc) ligating the oligonucleotide from steps aa) and ab) in the orientation determined by the blockage of the end that are not to be ligated(See Fig. 2A-3E for example and Col. 6 lines 35-55).

bd) removing non-consumed reactants and enzymes(Col. 20 lines 51-57) in a wash with TE(pH 8.0).

be) cleaving the ligation product from step bc) with a type IIS restriction enzyme which cleaves outside its recognition sequence whereby the cleavage occurs in the nucleic acid sequence of the oligonucleotide from step ab)(Col. 13 and 14) in the reference's teaching of the "target polynucleotides cleaved with the nuclease of the stepping adaptor may be ligated to a further set of cleavage adaptors A4, A5, and A6 which may contain nuclease recognition sites that are same or different than those contained in cleavage adaptors A1, A2, and A3"(Col. 14 lines40-45).

bf) separating the reaction mixture from the elongated oligonucleotide from step aa) obtained in step ae) in their teaching in Col. 22 lines 20-21 that following cleave the beads are washed 3 times in TE (ph 8.0).

bg) repeating steps bb) to bf) at least once is taught throughout the reference and specifically in DuBridge's claim 4 teaching that the process be "repeated one or more times"(Col. 25 and claim 4).

c) ligating the oligonucleotide from steps a) and b) in the orientation determined by the blockage of the end that are not to be ligated(See Fig. 2A-3E for example and Col. 6 lines 35-55).

d) removing non-consumed reactants and enzymes(Col. 20 lines 51-57) in a wash with TE(pH 8.0).

e) cleaving the ligation product from step c) with a type IIS restriction enzyme which cleaves outside its recognition sequence whereby the cleavage occurs in the nucleic acid sequence of the oligonucleotide from step a) or step b)(Col. 13 and 14) in the reference's teaching of the "target polynucleotides cleaved with the nuclease of the stepping adaptor may be ligated to a further set of cleavage adaptors A4, A5, and A6 which may contain nuclease recognition sites that are same or different than those contained in cleavage adaptors A1, A2, and A3"(Col. 14 lines40-45).

f) separating the nucleic acid molecule elongated in this manner from the reaction mixture in their teaching in Col. 22 lines 20-21 that following cleave the beads are washed 3 times in TE (ph 8.0).

Regarding claim 22, considering the indefiniteness rejection, the art is interpreted to teach this limitation, as the oligonucleotide used in step ab) or bb) is a nucleic acid molecule.

Regarding claim 23, the method of claim 21 wherein an exonuclease and/or phosphatase reaction is carried out as step ac), bc), or c) after step ac), bc) or c) is taught throughout but specifically in Col. 20 lines 62-65, "the 5' phosphate is removed by treating the bead mixture with an alkaline phospatase".

Regarding claim 24, the method of claim 21 wherein the reaction mixture of step ac'), bc)' or c)' is removed after the reaction also in Col. 20 lines 55-57 in the washing step with TE.

Regarding claim 25, the method of claim 21 where the recognition sequence and the other part of the recognition sequence for this restriction enzyme is derived from the oligonucleotide from step ab), bb) or b)(Col. 13 and 14 any one of A1, A2, A3 or the "stepping adaptor" references) which is at least partially double stranded(col. 3 line 26 for example) and contains a different recognition sequence than in step ba) for a type IIS restriction enzyme which cleaves outside its recognition sequence, whereby this oligonucleotide cannot bind the matrix, in their teaching of "many target polynucleotides in parallel" and "attaching a first oligonucleotide tag from a repertoire of tags to each polynucleotide in a population of polynucleotides" and "further sampling the population of polynucleotides such that substantially all different polynucleotides in the population have different first oligonucleotide tags attached"(See Col. 11-12, and figures 2A-3E).

Regarding claim 26, the method of claim 21 wherein the modification is a biotin residue is taught in Col. 13 line 60, as "a biotin, or like moiety, could be employed to anchor the polynucleotide-encoded adaptor conjugate, as no sorting would be required".

Regarding claim 27, the method of claim 21 wherein the oligonucleotide from step aa), ba), or a) and/or ab), bb) or b) has a loop.(Col. 16 lines 1-4).

Regarding claims 29 and 30, the method of claim 21 wherein the solid matrix is a bead(Col. 19 and above) and wherein the matrix comprises commercially available CPG and polystyrene beads(e.g.available from Applied Biosystems, Foster City, CA).

Regarding claims 31 and 32 the method wherein the oligonucleotides are complementary and the overhangs are 1, 2, 3, 4, or 5 nucleotides long, is taught for example in Figures 2A-3E.

Dubridge et al. do not teach the method of claim 21 step bg) wherein the oligonucleotide linked to the solid support is cleaved through a digest with type IIS restriction enzymes.

However, Church et al. teach replica amplification of nucleic acid arrays wherein "a nuclease recognizing the probe cuts the ligated complex at a site one or more nucleotides from the ligation site along the target polynucleotide leaving an end, usually a protruding strand, capable of participating in the next cycle of ligation and cleavage. An important feature of the nuclease is that its recognition site be separate from its cleavage site. In the course of such cycles of ligation and cleavage, the terminal nucleotides of the target polynucleotide are identified. As stated above, one such category of enzyme is that of type IIs restriction enzymes, which cleave sites up to 20 base pairs remote from their recognition sites; it is contemplated that such enzymes may exist which cleave at distances of up to 30 base pairs from their recognition sites.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of DuBridge et al. with that of Church et al. for the expected benefit of creating a truncation nucleic acid that would now be "capable of participating in the next cycle of ligation and cleavage"(Col. 19 and 20) in the production of additional DNA fragments.

3. Claim 28 is rejected under 35 U.S.C. 103(a) as being unpatentable over DuBridge et al.(US Patent 5,888,737) in view of Church et al.(US Patent 6,485,944) as applied to claim 21 above and in further view of Lane et al.(US Patent 5,770,365).

While the teachings of DuBridge et al.(US Patent 5,888,737) in view of Church et al.(US Patent 6,485,944) are summarized above, they do not teach the method of claim 21 wherein the oligonucleotide from step aa), ba) or a) is coupled via a modification in the loop region to the solid matrix.

However, Lane et al. teach nucleic acid capture moieties that in FIG.1 "illustratively shows the hairpin 10 immobilized to an insoluble support 15 through a spacer moiety 12"(Col. 6 lines 44-57).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of DuBridge et al. in view of Church et al. and in further view of Lane et al. for the expected benefit of covalently linking "sequences B and D together and positions them (e.g. holds them in sufficiently close proximity) such that a B:D intramolecular duplex can form"(Col. 6 lines 51-54).

4. Claim 33 is rejected under 35 U.S.C. 103(a) as being unpatentable over DuBridge et al.(US Patent 5,888,737) in view of Church et al.(US Patent 6,485,944) as applied to claim 21 above and in further view of Israel(US Patent 5,981,190).

While the teachings of DuBridge et al.(US Patent 5,888,737) in view of Church et al.(US Patent 6,485,944) are summarized above, they do not teach the method of claim 21 wherein the

various type IIS restriction endonucleases are replaced by ribozymes which cleave in an analogous manner.

However, Israel teaches the analogous manner of using ribozymes and type IIS restriction enzymes in their teaching of type IIS enzymes followed by the teaching that "other methods for cleaving the sample nucleic acid at predetermined sequences include the use of ribozymes"(Col. 11 lines 7-9).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the method of DuBridge et al. in view of Church et al. and in further view of Israel since ribozymes are taught by applicant and by Israel to act in an analogous manner as type IIs restriction enzymes.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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4/19/04

EJ FORMAN, PH.D.
PRIMARY EXAMINER